amount sufficient to reduce the condition associated with fetal alcohol syndrome, wherein the ADNF polypeptide is a member selected from the group consisting of:

(a) an ADNF I polypeptide having the following amino acid sequence:

$(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:3);

(b) an ADNF III polypeptide having the following amino acid sequence:

$(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:4);

(c) a mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b);

wherein R^1, R^2, R^3, and R^4 are independently selected and are an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected; and

x, y, w, and z are independently selected and are equal to zero or one.

18. (Once amended) The method of claim 1, wherein the condition is likelihood of death of the subject *in utero*.

REMARKS

With this amendment, Claims 1, 4-13 and 15-18 are pending. Claims 19-44 are currently withdrawn from consideration as being drawn to non-elected inventions and have been canceled without prejudice. For convenience, the Examiner's rejections are addressed in the order presented in the June 3, 2002 Office Action. Appendix A provides the version with markings to show changes made to the claims. Also for the Examiner's convenience, Appendix B is included, listing all pending and amended claims.

I. Status of the Claims

Claim 1 is amended to read administration of ADNF to a subject while *in utero*. Support for this amendment is found, for example, at page 17, lines 4-7. This amendment adds no new matter.

Claim 18 is amended to read that the condition being reduced is the likelihood of death of the subject *in utero*. Support for this amendment is found, for example at page 19, lines 25-27. This amendment adds no new matter.

II. Rejection Under 35 U.S.C. §112, First Paragraph: Enablement

Claims 1, 4-13, and 15-18 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to provide enablement for reducing a condition associated with fetal alcohol syndrome. The standard for enablement cited by the Examiner is that the specification must enable one skilled in the art to be able to make and use the invention commensurate in scope with the claims. The Examiner does state that the specification is enabling for a method for inhibiting fetal demise, decreased fetal birth weight, decreased fetal brain weight, and decreased levels of VIP mRNA in a subject exposed to alcohol *in utero* by administration of ADNF peptides prior to alcohol exposure.

While Applicants believe the specification fully enables the claims as written, in order to expedite prosecution and permit the earliest possible date of allowance, Applicants have amended claim 1 to read administration of ADNF to a subject while *in utero*. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner has raised two objection to based on enablement. First the Examiner alleges that the application is enabled for treating only for exemplified conditions associated with fetal alcohol syndrome, *e.g.*, fetal demise, decreased fetal birth weight, decreased fetal brain weight, and decreased levels of VIP mRNA; rather than the full range of fetal alcohol associated conditions. The Examiner also alleges that the application does not enable variations of exemplified methods of administration of ADNF peptides to treat conditions associated with fetal alcohol syndrome. The variations include non-exemplified timing of administration and dosages of ADNF peptides.

A. The application is enabled for reducing conditions associated with fetal alcohol syndrome.

The claimed invention is a method to treat fetal alcohol syndrome by administering ADNF peptides to a subject exposed to alcohol while *in utero*. The Examiner and Applicants are in agreement that the rodent model used test ADNF peptides is an art-accepted model. Office Action at page 3. However, the Examiner alleges that only the conditions exemplified to be reduced by ADNF treatment in the specification; *e.g.*, likelihood of fetal demise, decreased fetal birth weight, and decreased fetal brain weight; are enabled by the specification. In addition, the Examiner appears to be concerned about the possibility of inoperative embodiments.

1. The art-accepted rodent model used by applicants correlates with fetal alcohol syndrome.

The Examiner alleges there are no working examples for reduction of conditions associated with fetal alcohol syndrome other than those exemplified. Applicants respectfully disagree and state that the rodent model described in the specification correlates with the claimed method of treating fetal alcohol syndrome.

According to the MPEP at 2164.02, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating to that condition, unless the Examiner has evidence that the model does not correlate. The issue is whether one of skill in the art would accept the model as reasonably correlating to the condition. *In re Brana,* 51 F.3d 1560, 1566 (Fed. Cir. 1995). In addition, the Federal Circuit has ruled that a rigorous or exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985).

Applicants presented evidence with the previous response that the rodent model is an art-accepted model that correlates with fetal alcohol syndrome. *See, e.g.*, Declaration of Dr. Brenneman. The specification provides ample evidence that ADNF

peptides are useful to treat fetal alcohol syndrome using the art-accepted rodent model. Because a rigorous or exact correlation between a model and a condition is not required, the examples provided by the Applicants are sufficient to enable treatment of fetal alcohol syndrome with ADNF peptides.

The conditions tested by applicants (*e.g.*, fetal survival, fetal birth weight, fetal brain weight and levels of VIP mRNA) are all widely recognized as symptoms of fetal alcohol syndrome. Using the art-accepted rodent model system, Applicants have shown that all tested conditions that are associated with fetal alcohol syndrome are reduced by administration of ADNF peptides. When considered as a whole, Applicants successful showing of reduction of symptoms of fetal alcohol syndrome by administration of ADNF peptides demonstrates that ADNF peptides can be used to treat fetal alcohol syndrome as claimed. In addition, the Examiner has not met his burden under MPEP at 2164.02 to provide evidence that the art-accepted rodent model does not correlate with fetal alcohol syndrome as a whole. Thus, the rejection for non-enablement is improper and should be withdrawn.

2. One of skill in the art would how to avoid inoperative embodiments given the guidance in the specification.

In addition, the Examiner appears concerned about inoperative embodiments and alleges that, unless all conditions associated with fetal alcohol syndrome are reduced by treatment with ADNF peptides, the method is inoperative. The Examiner also alleges that because not all conditions associated with fetal alcohol syndrome have been tested using the model system, treatment of fetal alcohol syndrome as a whole is not enabled.

The Examiner appears to have focused improperly on inoperative embodiments, leading to the conclusion that undue experimentation would be required to carry out the methods of the claimed invention. However, the proper test of enablement is "whether one skilled in the art could make or use the claimed invention from the

disclosure in the patent coupled with information known in the art without undue experimentation" (*see, e.g.*, MPEP §2164.01).

The Examiner appears concerned that the following conditions associated with fetal alcohol syndrome may not be affected by administration of ADNF peptides: changes in memory and learning, coordination, skeletal, facial, and brain deformities. However, the Examiner does not present evidence that the above-listed conditions are not affected by administration of ADNF peptides. The Examiner also appears to suggest that if the above-listed conditions are not affected by ADNF administration, the patient will not receive benefit from ADNF administration. Applicants have provided ample data to show that administration of ADNF peptides alleviates multiple fetal alcohol syndrome symptoms, *e.g.*, fetal demise, decreased fetal birth weight, decreased fetal brain weight, and decreased levels of VIP mRNA. Thus, applicants have demonstrated that ADNF administration is an effective treatment of fetal alcohol syndrome. In the present application, one of skill would know how to avoid inoperative embodiments and use ADNF peptides to treat conditions associated with fetal alcohol syndrome without undue experimentation (*see, In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). Moreover, the present application provides guidance in the form of assays and working examples for treatment of conditions associated with fetal alcohol syndrome.

B. Variations of the exemplified methods are enabled by the application.

The Examiner alleges the specification enables treatment of fetal alcohol syndrome only by the exemplified administration of ADNF peptide thirty minutes before alcohol ingestion and only at the exemplified dosages. To the extent the rejection applies to the claims as amended, Applicants respectfully traverse.

The Examiner has improperly imported a limitation from an example into the claims. The Federal Circuit Court of Appeals and the Patent Office agree that claims are to be interpreted in light of the specification, and given their broadest interpretation. Limitations found in the specification are not to be read into the claims. MPEP 2164.08

and *Raytheon v. Roper Corp.*, 724 F.2d 951 (Fed. Cir. 1983). Claims are not to be rejected as broader than the enabling disclosure for non-inclusion of limitations within the ordinary level of skill in the art.

The USPTO has also spoken on this issue in the Training Materials for Examining Applications With Respect to 35 U.S.C. §112, First Paragraph-Enablement-Chemical/Biotechnical Applications. " If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. Section 112, is satisfied." Training Materials at III.A.2.b.ii., citing *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); and *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). Thus, "[i]t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." Training Materials at III.A.2.b.ii.

The Examiner asserts that administration of ADNF peptides after birth to an individual exposed to alcohol *in utero* would not affect a condition associated with fetal alcohol syndrome. In order to expedite prosecution, Applicants have amended Claim 1 to read administration of ADNF to a subject while *in utero*. Support for this amendment is found, for example, at page 17, lines 4-7.

1. The application is enabled for treatment of fetal alcohol syndrome with ADNF peptides before and after administration of alcohol.

Applicants disclose a general method of reducing conditions associated with fetal alcohol syndrome by administering ADNF peptides. Although Applicants did not specify an essential or even a preferred timing of administration of the ADNF peptides, the Examiner asserts that Applicants are entitled only to claim scope that corresponds to an exemplified administration treatment of fetal alcohol syndrome with ADNF peptides, *e.g.*, administration of ADNF peptides 30 minutes prior to alcohol ingestion. The Examiner has improperly imported a limitation from an example into the

claims. Under the Examiner's suggested claim scope, Applicants will not receive the benefit of the claim scope they are entitled to by law. The suggested claim scope eliminates coverage of variations of the example provided by Applicants, even though those variations are within the guidelines of the specification and considered routine experimentation by those of skill in the art. For example, under the Examiner's suggested claim scope, Applicants are entitled to protection only from infringers that use ADNF peptides to treat fetal alcohol syndrome 30 minutes before ingestion of alcohol. Thus, according to the Examiner, Applicants are not entitled to protection from infringers that use ADNF peptides to treat fetal alcohol syndrome 3 hours after ingestion of alcohol, one hour after ingestion of alcohol, 29 minutes before ingestion of alcohol, or 31 minutes before ingestion of alcohol.

Applicants assert that the timing of administration of ADNF peptides would not require undue experimentation by one of skill in the art. Applicants provide a model system for testing treatment of fetal alcohol syndrome with ADNF peptides. The examples of treatment of fetal alcohol syndrome by administration of ADNF peptides 30 minutes before alcohol ingestion can be used as guidance to determine other appropriate times for administration of ADNF peptides. At the time of filing, those of skill in the art would have recognized that treatment of fetal alcohol syndrome by the methods of the claimed invention was not limited to administration of ADNF peptides 30 minutes before alcohol ingestion and that methods to determine the timing of administration were within their skill level.

2. The application is enabled for treatment of fetal alcohol syndrome with appropriate dosages of ADNF peptides.

As discussed above, Applicants disclose a general method of reducing conditions associated with fetal alcohol syndrome by administering ADNF peptides. Although Applicants did specify dosage ranges for administration of ADNF peptides to mice and pointed out methods available to extrapolate those dosages to humans (see, *e.g.*,

specification at page 19, lines 19-22), the Examiner asserts that Applicants are entitled only to claim scope that corresponds to an exemplified treatment of fetal alcohol syndrome with ADNF peptides, *e.g.*, administration of 40 μg ADNF peptides 30 minutes prior to alcohol ingestion.

Applicants respectfully traverse the rejection. As above, the Examiner has improperly limited the claims by importing a limitation from an example into the claims. The Examiner eliminates coverage of variations of the example provided by Applicants, even though those variations are within the guidelines of the specification and considered routine experimentation by those of skill in the art. Under the Examiner's suggested claim scope, Applicants will not receive the benefit of the claim scope they are entitled to under U.S. patent law.

Applicants assert that optimization of the dosage of ADNF peptides would not require undue experimentation by one of skill in the art. Applicants provide a model system to determine an appropriate dosage of ADNF peptide and guidance to extrapolate from the model system to human subjects (see, *e.g.*, specification at page 19, lines 19-22). At the time of filing, those of skill in the art would have recognized that treatment of fetal alcohol syndrome by the methods of the claimed invention was not limited to the exemplified dosage of ADNF peptides and that methods to determine the timing of administration were within their skill level.

In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

III. Rejection Under 35 U.S.C. §112, Second Paragraph: Written Description

Claim 18 is rejected under 35 U.S.C. §112, second paragraph as allegedly failing to point out and distinctly claim the subject matter regarded by the applicant as the invention. To the extent the rejection applies to the amended claim, Applicants respectfully traverse the rejection.

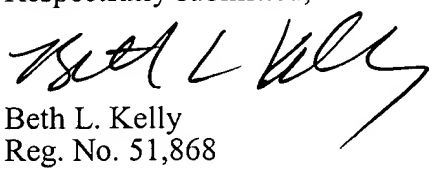
Claim 18 is amended to recite that the condition being reduced is the likelihood of death of the subject *in utero*. Support for this amendment is found, for example at page 19, lines 25-27. In view of the amendment, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Thrice amended) A method for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*, the method comprising administering to the subject while *in utero* an ADNF polypeptide in an amount sufficient to reduce the condition associated with fetal alcohol syndrome, wherein the ADNF polypeptide is a member selected from the group consisting of:

(a) an ADNF I polypeptide having the following amino acid sequence:

$(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:3);

(b) an ADNF III polypeptide having the following amino acid sequence:

$(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:4);

(c) a mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b);

wherein R^1, R^2, R^3, and R^4 are independently selected and are an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected; and

x, y, w, and z are independently selected and are equal to zero or one.

18. (Once amended) The method of claim 1, wherein the condition is likelihood of death of the subject *in utero*.

APPENDIX B
PENDING AND AMENDED CLAIMS

1. (Thrice amended) A method for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*, the method comprising administering to the subject while *in utero* an ADNF polypeptide in an amount sufficient to reduce the condition associated with fetal alcohol syndrome, wherein the ADNF polypeptide is a member selected from the group consisting of:

(a) an ADNF I polypeptide having the following amino acid sequence:

$(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:3);

(b) an ADNF III polypeptide having the following amino acid sequence:

$(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:4);

(c) a mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b);

wherein R^1, R^2, R^3, and R^4 are independently selected and are an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected; and

x, y, w, and z are independently selected and are equal to zero or one.

4. (Once amended) The method of claim 1, wherein for the ADNF I polypeptide x and y are both zero.

5. (Once amended) The method of claim 1, wherein for the ADNF I polypeptide:

x is one;

R^1 is Val-Leu-Gly-Gly-Gly (SEQ ID NO:5); and

y is zero.

6. (Once amended) The method of claim 1, wherein for the ADNF I polypeptide:

x is one;

R^1 is Val-Glu-Glu-Gly-Ile-Val-Leu-Gly-Gly-Gly (SEQ ID NO:6); and

y is zero.

7. (Once amended) The method of claim 1, wherein for the ADNF III polypeptide w and z are both zero.

8. (Once amended) The method of claim 1, wherein for the ADNF III polypeptide:

w is one;

R^3 is Gly-Gly; and

z is zero.

9. (Once amended) The method of claim 1, wherein for the ADNF III polypeptide:

w is one;

R^3 is Leu-Gly-Gly;

z is one; and

R^4 is Gln-Ser.

10. (Once amended) The method of claim 1, wherein for the ADNF III polypeptide:

w is one;

R^3 is Leu-Gly-Leu-Gly-Gly (SEQ ID NO:7);

z is one; and

R^4 is Gln-Ser.

11. (Once amended) The method of claim 1, wherein for the ADNF III polypeptide:

w is one;

R^3 is Ser-Val-Arg-Leu-Gly-Leu-Gly-Gly (SEQ ID NO:8);

z is one; and

R^4 is Gln-Ser.

12. (Once amended) The method of claim 1, wherein the ADNF polypeptide is a mixture of ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b).

13. (Once amended) The method of claim 1, wherein x, y, w, and z are all zero.

15. (As filed) The method of claim 1, wherein the condition is a decreased body weight of the subject.

16. (As filed) The method of claim 1, wherein the condition is a decreased brain weight of the subject.

17. (As filed) The method of claim 1, wherein the condition is a decreased level of VIP mRNA of the subject.

18. (Once amended) The method of claim 1, wherein the condition is likelihood of death of the subject *in utero*.